Instead, we compared the rates of response to LCBI and salvage chemotherapy after immunotherapy after dividing chemotherapy regimens into pemetrexed/platinum, taxane based, gemcitabine based, and others.

In conclusion, though it is a retrospective study with a small number of subjects, we think that our study was well conducted with reasonable methods and provides clinical evidence for future prospective trials that will investigate the improved clinical outcomes of salvage therapy after immune checkpoint inhibitors.

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Comments on Prognostic Impact of Margin Distance and Tumor Spread through Air Spaces in Limited Resection for Primary Lung Cancer

To the Editor:

We read with great interest the study by Masai et al.[1] The authors mentioned that spread through air spaces is associated with local recurrence with a hazard ratio (HR) of 12.24 (95% confidence interval [CI]: 2.61–57.37) and, moreover, lymph vessel invasion is associated with distant recurrence (HR = 8.36, 95% CI: 1.67- 41.87).[1] Although the results were very interesting, some methodological issues should be considered.

It argued that relatively large effect estimate and imprecise CI may be obvious indicators of sparse data bias.[2–4] In other words, there are inadequate data for combination of predictor and outcome levels.[2] Here, we are concerned that the estimated HRs (and 95% CIs) for spread through air spaces and lymph vessel invasion may be biased because of sparse data bias.

Another important reason for imprecise CI for estimate coefficients is presence of collinearity among the studied predictors. As a general rule, collinearity among the predictors will be checked before regression analysis by using variance inflation factors.[5]

The authors did not attempt to check the proportional hazards assumption before Cox regression analysis. As shown in the Figure 1 of Masai et al,[1] it may be that the proportional hazards assumption is violated

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for relapse-free survival curves for local recurrence of patients undergoing limited resection according to the studied variables.

Finally, it seems that there is degree of referral bias in the estimated associations on account of selection of patients referred to the National Cancer Center Hospital for the study.

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Response to Letter to the Editor Titled "Comments on Prognostic Impact of Margin Distance and Tumor Spread through Air Spaces in Limited Resection for Primary Lung Cancer"

In Response:

We would like to thank Mansori et al.[1] for their interesting and thoughtful comments on our article "Prognostic Impact of Margin Distance and Tumor Spread through Air Spaces in Limited Resection for Primary Lung Cancer."[2]

As they pointed out, the small number of cases of disease recurrence and death in our study may have resulted in imprecise confidence intervals (CIs), which may have slightly diminished the reliability of the identified indicators of poor prognosis. We are aware of these limitations and have addressed them in the "Discussion" section of our article.[2] We also think it meaningful that two factors—the presence of tumor spread through air spaces (STAS) and a short surgical clearance distance (<1 cm)—were statistically significant as poor prognostic factors despite the small numbers of recurrences and deaths in our study cohort. It is likely that this small number of events is the main cause of the imprecise CIs.

To calculate variance inflation factors (VIFs), we reexamined our sample data by using SPSS software (IBM Corp., Armonk, NY). For the four local recurrence factors that were significant in univariate analysis—tumor margin, STAS, age, and tumor grade—the VIFs were 1.011, 1.198, 1.071, and 1.249, respectively. The VIFs for locoregional recurrence factors were 1.237 for STAS; 1.621 for tumor grade; 1.072 for tumor size; and 1.461, 1.553, and 1.780 for lymph vessel, vascular, and pleural invasion, respectively. Finally, for distant recurrence factors, the VIFs were 1.231 for STAS, 1.076 for age; 1.635 for tumor grade; and 1.540, 1.786, and 1.455 for lymph vessel, vascular, and pleural invasion,

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